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IRREVERSIBLE ELECTROPORATION FOR NONTHERMAL TUMOR ABLATION IN THE-clinical-setting: A SYSTEMATIC REVIEW OF SAFETY AND EFFICACY

Abstract

Introduction
Irreversible electroporation (IRE) is a novel, non-thermal tumor ablation technique that uses electrical pulses to induce cell death, whilst preserving structural integrity of bile ducts and vessels. This systematic review provides an overview of current clinical results.

Methods
All in-human literature on IRE reporting safety and/or efficacy was included. All adverse events were recorded. Tumor response on follow-up imaging from 3 months onwards was evaluated.

Results
In sixteen studies, 221 patients had 325 tumors treated in liver (n=129), pancreas (n=69), kidney (n=14), lung (n=6), lesser pelvis (n=1) and lymph node (n=2). No major adverse events during IRE were reported. IRE caused only minor complications in the liver, but three major complications in the pancreas (bile leak n=2, portal vein thrombosis n=1). Complete response at 3 months was 67-100% for hepatic tumors (93-100% for tumors <3cm). Pancreatic IRE combined with surgery lead to prolonged survival compared to control (20 vs 13 months) and significant pain reduction.

Conclusion
Where other techniques are unsuitable, IRE is a promising modality for the ablation of tumors near bile ducts and blood vessels. This review gives an extensive overview of the available evidence, which unfortunately is limited in terms of quality and quantity. With this in mind, IRE of central liver tumors seems relatively safe without major complications, whereas complications after pancreatic IRE appear more severe. The available limited results for tumor control are generally good. Overall, the future of IRE for difficult-to-reach tumors appears promising.
Introduction

In the past two decades, image-guided ablation for focal tumor treatment has received substantial attention when surgical options are precluded. The rapid development of ablative devices in the past years, has led to a continuous expansion of treatment options. Nowadays, tumor ablation has been accepted as a valuable adjunct to the traditional surgical, chemotherapeutic and radiation regimens (1). Different ablative techniques for the treatment of unresectable tumors are percutaneous ethanol injection, stereotactic ablative radiotherapy, and thermal ablation such as cryoablation, laser interstitial thermotherapy, high intensity focused ultrasound, microwave ablation and radiofrequency ablation (RFA). Recently, a new treatment method with certain advantages over the existing ablative techniques has gained widespread attention: irreversible electroporation (IRE). With IRE, cell death is induced with electrical energy. Under image-guidance, electrodes are placed around the tumor and through multiple short high-voltage electrical pulses, the existing cell membrane potential is disturbed (figure 1). As a consequence, nanoscale defects appear in the lipid bilayer of the cell membrane. Depending on the amplitude and duration of the pulses, the permeability of the cell membrane is reversible after which the cell survives, or irreversible after which the cell dies through loss of homeostasis(2). Although IRE is believed to effectively destroy all cells within the ablation zone, the non-thermal nature of IRE results in relative preservation of the extracellular matrix. As a result, the structural integrity of inlaying and adjacent tissue structures such as vessels and bile ducts remains intact. Moreover, treatment effect should not be impeded by heat-sink (2).

Numerous animal studies have investigated these hypotheses: indeed, the integrity of portal triad structures, bowel wall, pancreatic duct and urinary collecting system is guarded, due to sparing of the collagen scaffold, followed by regeneration (3–11). Following IRE around peripheral nerves, preservation of endoneural architecture and proliferation of Schwann cells may enable axonal regeneration with full function recovery (12,13). Most importantly, complete cell death has been confirmed throughout the ablation zone within hours after IRE(14), as well as significant tumor reduction of hepatic and pancreatic cancer xenografts in mice (8,15).

With these distinctive characteristics, IRE may be suitable for the treatment of tumors ineligible for surgical resection or thermal ablation due to unfavorable location. However, the local application of an excessive electric field is a potential hazard, since the pulses could induce cardiac arrhythmias and severe muscle contractions(16). The last two years, a growing experience with IRE in humans has been reported in the literature.

To investigate how the theoretical advantages of IRE are reflected in clinical practice, a
A systematic review was performed. Objectives were safety and efficacy in terms of complications, tumor response, survival and symptom reduction. The analyzed data should inform clinicians on the current position of IRE in interventional oncology, its indications for clinical use, and should provide researchers a compass for future clinical studies.

**Figure 1:** IRE-procedure of a centrally located colorectal liver metastasis (arrowhead). (a-c) F18-FDG PET-CT, ceCT and MRI-DWib800 pre-IRE images showing a small segment IV avid lesion abutting the middle hepatic vein (MHV) and approximate to the common bile duct (CBD) and portal vein (PV). (d,e) Percutaneous CT guided IRE procedure with electrodes in situ. (f) MRI-DWib800 24h post IRE showing a typical hypo-intense ablation zone surrounded by a hyperintense rim. (g-i) Imaging 3 months post IRE showing a vaguely demarcated hypodense scar lesion on ceCT, which becomes iso-intense on MRI-DWib800 and non-avid on F18-FDG PET-CT.
Methods

The review was written according to the PRISMA guidelines for reporting systematic reviews(17). The reviewers agreed to the terminology suggested in “Image-Guided Tumor Ablation: Standardization of Terminology and Reporting Criteria”(18).

Search strategy
A comprehensive systematic review of the literature published until November 2013 was performed using Embase and Medline (PubMed). Alternatively found studies were also checked for eligibility. MeSH search terms and keywords used in the search were: irreversible electroporation (IRE), electroporation, electropermeabilization and electrocoagulation.

In- and exclusion criteria
Studies were included if they met all of the following criteria: (1) human subject(s), (2) who underwent IRE, (3) of primary or secondary tumor(s), (4) investigating safety and/or efficacy. Exclusion criteria were: (1) review or meta-analysis, (2) abstract only. Studies of all designs in the English, French and German language were included. Two reviewers (KN and HJS) independently performed literature search, article inclusion, data extraction and quality assessment. When necessary the corresponding author was contacted to prevent analysis of overlapping study results.

Quality assessment
The Quality Assessment Tool for Quantitative Studies checklist was used to assess the quality of the included studies in terms of study design, risk of bias, confounders, blinding, data collection methods and withdrawals and drop-outs (http://ephpp.ca/PDF/Quality%20Assessment%20Tool_2010_2.pdf). Although a dedicated assessment tool for case reports does not exist, this checklist includes valuable criteria that apply to case reports as well. Furthermore, the level of evidence of each article was scored according to the system for assigning level of evidence from the Centre for Evidence-Based Medicine (CEBM) in Oxford, UK(19). The levels of evidence range from 1 (strong evidence) to 5 (weak evidence). Discrepancies were resolved by consensus.

Data extraction
From each article, the clinical indication for IRE was noted. Other baseline characteristics were: treated organ and tumor type, previous treatments, ablation approach and additional surgical procedures.

For safety assessment, all adverse events during IRE, related to the direct application of
strong electric field, electrode placement, or any other adverse event were recorded, as well as all adverse events during follow-up. When mentioned by the original authors, complications were divided in IRE-related and not IRE-related, and graded according to the Common Terminology Criteria of Adverse Events (CTCAE) version 3.0(20). CTCAE grade ≥3 was considered a major complication. When not provided, the reviewers addressed a grade only if it could be clearly derived from the text, which meant that treatment as well as outcome after treatment were explicitly stated (e.g. if the authors stated “resolving spontaneously” or “requiring chest drainage”). If uncertainty remained, no grade was addressed.

Despite a lack of consensus on a standard follow-up interval regimen for imaging, a period of at least 3 months is commonly suggested the minimum to allow for meaningful efficacy analysis (18). Primary technique effectiveness was defined as the percentage of tumors successfully eradicated following the initial procedure based on follow-up imaging after 3 months(18); secondary technique effectiveness was defined as successful tumor eradication from 6 months onwards after the first treatment (successful repeat ablation included). Other outcomes reported were overall survival, local progression-free survival (LPFS) and distant progression-free survival (DPFS). Treatment effect of pancreatic ablation was specified as stable disease, local progression and/or distant progression, and significant symptom reduction after at least 3 months. Studies (or patients) with follow-up <3 months were excluded from efficacy analysis.

Results

The searches identified 232 hits in Pubmed and 353 in Embase. After removal of duplicates and exclusion based on title and abstract, the manuscripts of 26 remaining articles were reviewed. Sixteen full-text articles remained for analysis (figure 2). The articles were published between August 2010 and November 2013. Six articles were case reports and ten articles were case series. In figure 3 the quality assessment summary scores of the included studies are shown. The entire list of ratings for each study is available in the electronic supplement (appendix A, available online at www.jvir.com). All studies were classified as level of evidence 4. Martin et al assessed safety of pancreatic IRE (n=27)(21) and subsequently assessed efficacy (n=54)(22). Since the patients in these articles overlapped, the first article was used for safety analysis only and the second for efficacy analysis only. Thomson et al assessed safety and early efficacy in 37 patients with hepatic, renal and lung tumors(23). Cheung et al later reported longer follow-up results for eleven patients within this patient group with HCC specifically(24). These eleven HCC patients were excluded for
analysis from the article of Thomson et al. Similarly, Kingham et al (25) treated 28 patients with 65 perivascular hepatic tumors. Silk et al later reported the results of eleven patients that had 22 peribiliary hepatic metastases treated (26), of which two patients with three tumors overlapped with Kingham et al. These two patients were excluded for analysis in the article from Silk et al.

Patient characteristics
In total, 221 patients with 325 lesions in different organs were treated: 227 hepatic tumors (n=129; 49 HCC, 57 CRLM, 23 other), 70 unresectable pancreatic adenocarcinoma (n=69; 41 head, 27 body/tail, 1 uncinate process), 17 renal tumors (n=14; 10 RCC, 4 other), 8 pulmonary tumors (n=6; all different origin), one presacral tumor (metastatic endometrial carcinoma) and two lymph nodes (n=2). The majority of the patients was heavily pretreated and underwent IRE due to tumor proximity to bile ducts, bronchi, renal pyelum, presacral neural plexus or large vessels, making it unsuitable for surgery or thermal ablation. In four studies, concurrent surgical procedures were performed during open IRE (21,25,27,28) and in one study concurrent thermal ablations were performed during percutaneous hepatic IRE (26). Patient characteristics are shown in table 1.

Procedure characteristics
All procedures were performed under general anesthesia. Treatment approach was open in 42.5% (94/221), laparoscopic in 1.8% (4/221) and percutaneous in 55.7% (123/221). Fourteen studies emphasized administration of muscle relaxants prior to ablation (21–34). Fifteen studies described the use of ECG gating (21–35). The heterogeneity of reporting details such as inter-electrode distance, applied voltage and resulting current, pulse duration, number of electrodes and repositionings did not allow for a detailed review of these parameters.
Figure 2 Flow diagram of literature search and article selection.

Records identified through database searching
  PubMed n=133
  Embase n=108

Additional records through other sources
  n=0

Removal of duplicates
  n=155

Exclusion based on title and/or abstract
  n=308

No full text available
  n=15

Exclusion based on full text
  n=11

Articles included for analysis
  n=12
  • Prospective clinical series (n=3)
  • Retrospective clinical series (n=5)
  • Case report (n=4)

Reasons for final exclusion:
  • Not assessing safety or efficacy (n=5)
  • Assessing imaging characteristics only (n=2)
  • [Potentially] overlapping study populations (n=4)

Figure 3 Graph showing the quality assessment summary of the included studies. Note. – A = Selection bias; B = Study design; C = Confounders; D = Blinding; E = Data collection analysis; F = Withdrawals and drop-outs.
Safety
Due to overlapping patient series in the articles from Martin et al (21,22), adverse events were available for (194/221) patients. Not IRE-related complications were most commonly associated with open surgical procedures, as stated by the authors and are not displayed in this review (21,28). In total, 43 possibly or certainly IRE-related complications were noted. Complication rate per organ was 16% (21/129) for liver, 19% (8/42) for pancreas, 36% (5/14) for kidney and 50% (3/6) for lung. In 5/43 complications the treated organ was unknown. Most complications (28/43; 64%) were CTCAE grade I/II. Grade III, IV and V complications (3/43; 7%) were only reported after pancreatic IRE. For 12/43 complications, grade was unknown (29%). Adverse events are displayed in table 2.

Mortality
There were no per-procedural mortalities. Three mortalities were reported within 3 months after IRE (3/194), each after pancreatic IRE. Of these, one death was likely related to IRE-treatment, resulting in a mortality rate of 2.3% for pancreatic IRE (1/43). This patient had pre-existing portal vein thrombosis and underwent open IRE alongside a palliative bypass procedure. He presented with worsening ascites, hepatic and renal failure and died on day 70(21). Presumably, edema after ablation had contributed to progression of portal vein thrombosis. The other two mortalities were reported by the authors to be not directly attributable to IRE(34).

Complications related to electric pulses
Expected adverse events associated with the delivery of strong electric pulses are cardiac arrhythmias and severe muscle contractions. To prevent this, pulses are generally delivered in the refractory period of the heart, and with deep muscle paralysis. Eight arrhythmias were reported (CTCAE grade I-II), corresponding to a total incidence of 4% (8/194). Without synchronized pulsing, ventricular arrhythmias occurred four times (transient ventricular tachycardia), immediately resolving after pulse delivery abortion(23). With the use of cardiac synchronization only atrial arrhythmias occurred (n=4), resolving spontaneously or within 24 hours after therapy. With the administration of muscle relaxants, no uncontrolled muscle contractions were reported(21–34). Thomson et al were the only ones to report a transient increase in systolic blood pressure in all patients directly after IRE (20-30mmHg), which normalized spontaneously(23).

Site-related complications
No major complications were reported regarding hepatic IRE. Direct puncture-related complications were grade I and II pneumothorax (n=2), pleural effusion (n=1) and grade II
hemothorax (n=1)(23,30). Most lesions were located close to portal vessels or bile ducts. Stenosis or occlusion of these structures was reported in 8/129 treated patients (6%). Silk et al evaluated biliary complications after IRE of 19 liver metastases in 9 patients within 1cm of the common, left or right hepatic duct(26). One patient showed subsegmental bile duct prominence without increased bilirubin. This still existed after 11 months, without progressive dilatation or segmental atrophy. Retrospective review of CT images showed that one needle was placed in direct contact with the bile duct. Two other patients showed bile duct dilatation with increased bilirubin, for which one required stent placement; both conditions appeared to be secondary to tumor progression. Kingham et al treated 28 patients with 65 tumors of which the majority was located less than 1cm from a major hepatic vein or portal pedicle(25). Complications were grade I portal vein thrombosis, portal vein and bile duct occlusion (grades not provided), each after ablation within 0.5cm from a major portal pedicle. Other complications were biliary stent occlusion and cholangitis(28). Ablation of an HCC near a transjugular intrahepatic porto-systemic shunt (TIPSS) did not cause occlusion or destruction of the shunt(32). Retrospective comparison of postprocedural pain after hepatic IRE and RFA showed similar moderate pain intensity with comparable amounts of self-administered pain medication(30).

Pancreatic IRE had an overall complication rate of 19% (8/42) and major complication rate of 7% (3/42). Direct complications were a spontaneous pneumothorax during anesthesia requiring chest drainage and a small subcutaneous hematoma(34). On follow-up, five site-specific complications occurred. Two were portal vein thrombosis after open IRE; one required paracentesis and aldactone, one was fatal(21). Furthermore, two cases of bile leak (CTCAE grade III-IV) were reported after open IRE(21); one patient had undergone concurrent duodenal stent removal via duodenotomy, in the other patient the electrodes were placed transduodenally. Both complications required percutaneous drainage after which they resolved. Pancreatitis was reported only once in 42 procedures, resolving spontaneously (CTCAE grade II)(34). Of note, Martin et al reported elevated amylase and lipase in all 27 patients, without clinical signs of pancreatitis(21). Abdominal pain grade I was reported in all patients (15/15) after percutaneous pancreatic ablation(34,35). Pain was always easily manageable with oral or intravenous analgesics and did not lead to prolonged hospitalization.

Besides one minor arrhythmia(27), renal IRE was complicated by accidental adrenal ablation leading to severe postural hypotension for 2 months(23). One ureter that was previously damaged by RFA required stenting after IRE, but no stricture was observed in the other six patients in whom the ureter or collecting system was within the treatment zone. Central IRE
caused transient hematuria in two patients (23).
Although lung tumors were located close to pulmonary arteries and azygos vein, lobar bronchi and the trachea, only one unexpected minor complication occurred (grade 1 parenchymal hemorrhage) (36). Furthermore, two of six lung ablations were associated with self-limiting pneumothorax, which is an expected event after lung ablation (23).
One patient was treated for palliative purposes for a large presacral recurrence of endometrial carcinoma (>2000 cm³), infiltrating the sacral bone and neural plexus causing severe pain (33). IRE was performed in two sessions. There was only mild paresis resolving spontaneously (grade I) and no sensory loss or impaired bladder function occurred. Opiate medication was withdrawn. Eight weeks later tumor volume had reduced to 791 cm³.

Efficacy
In three studies follow-up after hepatic IRE was not reported or was less than 3 months (30-32). So, 106 patients with 185 liver tumors were analyzed for efficacy: 27 HCC, 56 CRLM, 23 other malignancies (see table 3). No deaths due to disease progression were reported. Median tumor size varied from 1.0-3.0 cm (range 0.5-8.8 cm). Median follow-up period ranged from 3 to 18 months. Primary technique effectiveness varied from 67-100%, secondary technique effectiveness was 55-93% (some tumors were successfully retreated). Several authors reported an increased recurrence risk for larger tumors (23–26,28): Cheung et al. achieved 93% ablation success for tumors < 3 cm, and 100% for tumors < 2 cm at 18 months (p=0.003) (24) and Cannon et al reported 98% efficacy for tumors < 3 cm at 12 months (28). Silk et al. described local tumor recurrence in five of nine patients, with a median tumor size of 3.0 cm (26). Notably, 44% of the tumors treated by Kingham et al were located less than 0.5 cm from a major portal vein and 14% were located 0.6-1 cm from a major portal vein, which implied a relative contra-indication for RFA due to the probability of heat-sink induced recurrence. Technique effectiveness at 6 months was 93% (25). Similarly, IRE near the right portal vein (n=2) and the middle hepatic vein (n=1) was successful for 2 of 3 HCCs treated by Cheung et al. (24). The tumor that showed residual disease measured 6.1 cm.
Martin et al. performed open IRE with concurrent surgical procedures for locally advanced pancreatic carcinoma in 54 patients, in combination with chemoradiation (22). Results were compared to a matched patient group receiving chemoradiation only. Improved LPFS (14 vs. 6 months, p=0.01), DPFS (15 vs. 9 months, p=0.02), and overall survival (20 vs. 13 months, p=0.03) were demonstrated in the IRE-group. In case of progressive disease, most patients had distant progression. After a follow-up of approximately 20 months, no difference between the groups remained due to rapid progression of distant disease. Additionally, median pain score dropped from 5/10 to 3/10 (p=0.04), with a reduction of overall narcotic...
use ($p=0.03$). Quality-of-life scores were not registered. Narayanan et al treated three patients with metastatic disease at the time of IRE, all of whom died due to progressive metastatic disease after 3, 4 and 9 months (34). Of the patients with locally advanced disease, local progression occurred at 1 and 7 months (2/7) and distant progression at 4 months (1/7). Two patients underwent successful resection of the ablated lesion at 4 and 5 months and did not show evidence of disease at last follow-up after 11 and 14 months respectively. The remaining two patients had stable disease at 4 and 6 months. Results are shown in table 4.

Thomson et al(23) performed IRE of 11 renal tumors in 8 patients (7 RCC, 4 other tumors). Median tumor size was 2.7 cm (1.6-5.3). Primary technique effectiveness was 45% (5/11). Complete response was only noted for RCC.

Two studies reported on IRE of 8 pulmonary tumors in 6 patients from different origin(23,36). Median tumor size was 2.6 cm (2.0-8.4). After a follow-up of 3 to 12 months, all patients had progressive disease, of which one patient had died.

Table 1 Patient characteristics (page 121-122)

Note. – Perc = percutaneous; Lap = laparoscopic; CT = chemotherapy; RT = radiotherapy; CRT = chemoradiotherapy; ns = not specified; TIPSS = transjugular intrahepatic porto-systemic shunt; TACE = trans-arterial chemo embolization. *

Overlapping patient series: (21) reporting safety (n=27), (22) reporting efficacy (n=54). For safety analysis (21) is used, for efficacy analysis (22) is used.

Table 2 Adverse events of IRE (page 123-124)

Note. – Perc = percutaneous; VT = ventricular tachycardia; SVT = supraventricular tachycardia; AF = atrial fibrillation; ns = not specified. # Only observed prior to the use of cardiac synchronization. ‡ Leading to severe postural hypotension for 2 months. * See table 1
<table>
<thead>
<tr>
<th>Reference</th>
<th>Target organ</th>
<th>Number of patients</th>
<th>Number of lesions</th>
<th>Age (median)</th>
<th>Tumor location</th>
<th>Approach</th>
<th>Concurrent procedures during IRE</th>
<th>Pre/post-IRE treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannon et al.(28)</td>
<td>Liver</td>
<td>44</td>
<td>48</td>
<td>60</td>
<td>100% adjacent to major vascular/biliary structures and/or organs</td>
<td>Open (14) Perc (28) Lap (2)</td>
<td>7 concurrent abdominal procedure (ns)</td>
<td>Pre-IRE: 72% CT/RT/ablation/resection</td>
</tr>
<tr>
<td>Cheung et al.(24)</td>
<td>&quot;</td>
<td>11</td>
<td>18</td>
<td>71</td>
<td>7/18 adjacent to major vascular/biliary structures and/or organs</td>
<td>Perc</td>
<td>-</td>
<td>ns</td>
</tr>
<tr>
<td>Kasivisvanathan et al.(29)</td>
<td>&quot;</td>
<td>1</td>
<td>1</td>
<td>61</td>
<td>Portal vein abutment and adjacent bowel</td>
<td>Perc</td>
<td>-</td>
<td>Pre-IRE: CT, resection</td>
</tr>
<tr>
<td>Kingham et al.(25)</td>
<td>&quot;</td>
<td>28</td>
<td>65</td>
<td>51</td>
<td>57% ≤ 1cm major hepatic vein, 40% ≤ 1cm major portal pedicle</td>
<td>Open (22) Perc (6)</td>
<td>2 perioperative pump chemotherapy</td>
<td>Pre-IRE: 86% CT Post-IRE: 71% CT</td>
</tr>
<tr>
<td>Narayanan et al.(30)</td>
<td>&quot;</td>
<td>21</td>
<td>29</td>
<td>61</td>
<td>82% &lt;0.5cm gallbladder, liver capsule or dome of diaphragm</td>
<td>Perc</td>
<td>-</td>
<td>Ns</td>
</tr>
<tr>
<td>Niessen et al.(31)</td>
<td>&quot;</td>
<td>1</td>
<td>1</td>
<td>61</td>
<td>Close to diaphragm and heart muscle</td>
<td>Perc</td>
<td>-</td>
<td>Pre-IRE: RFA</td>
</tr>
<tr>
<td>Niessen et al.(32)</td>
<td>&quot;</td>
<td>1</td>
<td>1</td>
<td>65</td>
<td>Adjacent to a TIPSS stent graft</td>
<td>Perc</td>
<td>-</td>
<td>Pre-IRE: failed TACE</td>
</tr>
<tr>
<td>Silk et al.(26)</td>
<td>&quot;</td>
<td>9</td>
<td>19</td>
<td>60</td>
<td>14% &lt;1cm CBD, 68% &lt;1cm primary bile duct</td>
<td>Perc</td>
<td>8 additional thermal ablation/IRE/embolization</td>
<td>Pre-IRE: surgery 100%, CT 91%, RT 9%, embolization 27%</td>
</tr>
<tr>
<td>Bagla et al.(35)</td>
<td>Pancreas</td>
<td>1</td>
<td>1</td>
<td>78</td>
<td>pancreatic body</td>
<td>Perc (1)</td>
<td>-</td>
<td>Post-IRE: CT</td>
</tr>
<tr>
<td>Martin et al.(21)</td>
<td>&quot;</td>
<td>27</td>
<td>27</td>
<td>61</td>
<td>15 head, 12 body/neck</td>
<td>Open (27)</td>
<td>8 partial Whipple, 13 bypass, 3 partial gastrectomy, 17 ns</td>
<td>Pre-IRE: 85% CT and CRT</td>
</tr>
<tr>
<td>Study</td>
<td>Volume</td>
<td>Procedure</td>
<td>Location(s)</td>
<td>En bloc</td>
<td>Partial</td>
<td>Technique(s)</td>
<td>Pre-IRE</td>
<td>Post-IRE</td>
</tr>
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<td>------------------</td>
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<td>----------------------------------------------------------------------------</td>
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<tr>
<td>Martin et al. (22)*</td>
<td>54</td>
<td>54</td>
<td>61</td>
<td>Open</td>
<td>Lap</td>
<td>35 head, 19 body/neck 19 partial Whipple, 35 bypass, 9 celiac plexus block, 27 ns</td>
<td>Pre-IRE:45% CT, 45% CRT Post-IRE: 69% CT, 19% CRT</td>
<td></td>
</tr>
<tr>
<td>Narayanan et al. (34)</td>
<td>14 15  57</td>
<td>6 head, 7 body, 1 uncinate process</td>
<td>Perc</td>
<td>-</td>
<td>Pre-IRE: 100% CT, 73% RT, 1x Whipple</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pech et al. (27)</td>
<td>Kidney</td>
<td>6 6 57</td>
<td>ns</td>
<td>Open</td>
<td>All nephrectomy 15 minutes after IRE</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Usman et al. (36)</td>
<td>Lung</td>
<td>2 2 33, 70</td>
<td>Close to pulm. arteries, lobar bronchi, azygos vein, trachea</td>
<td>Perc</td>
<td>-</td>
<td>Pre-IRE: surgery, cryoablation, RT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Niessen et al. (33)</td>
<td>Presacral</td>
<td>1 1 56</td>
<td>Presacral with infiltration of the sacral bone and nerve plexus</td>
<td>Perc</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thomson et al. (23)</td>
<td>Liver Kidney Lung Lymph node</td>
<td>13 8 4 2</td>
<td>ns</td>
<td>Adjacent to vital structures in most patients</td>
<td>Perc</td>
<td>-</td>
<td>Standard therapy not possible/unsuccessful</td>
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<tr>
<td>Subtotal</td>
<td>Liver Pancreas Kidney Lung Lesser pelvis Lymph node</td>
<td>129 69 14 6 1 2</td>
<td>227 70 17 8 1 2</td>
<td>Open (94)</td>
<td>Perc (123)</td>
<td>Lap (4)</td>
<td></td>
<td></td>
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<tr>
<td>Total</td>
<td>221</td>
<td>325</td>
<td>221</td>
<td></td>
<td></td>
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*Note: Lap = Laparoscopic, Perc = Percutaneous
<table>
<thead>
<tr>
<th>Target organ</th>
<th>Approach</th>
<th>No. Patients</th>
<th>No. complications (%)</th>
<th>Complication related to Electric pulses (grade)</th>
<th>Treatment site (grade)</th>
<th>Other (grade)</th>
<th>Intervention</th>
<th>Reference</th>
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<tr>
<td>Liver</td>
<td>Perc</td>
<td>11</td>
<td>4 (36%)</td>
<td>-</td>
<td>-</td>
<td>4 Urinary retention (II)</td>
<td>Transient urethral catheter</td>
<td>Cheung et al.(24)</td>
</tr>
<tr>
<td></td>
<td>Perc</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>None</td>
<td>Kasivisvanathan et al.(29)</td>
</tr>
<tr>
<td></td>
<td>Perc</td>
<td>21</td>
<td>3(14%)</td>
<td>-</td>
<td>Pneumothorax (I)</td>
<td>Hematotherax (II) Pneumothorax (II) Pleural effusion (ns)</td>
<td>None Thoracocentesis ns</td>
<td>Narayanann et al.(30)</td>
</tr>
<tr>
<td></td>
<td>Perc</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>None</td>
<td>Niessen et al.(31)</td>
</tr>
<tr>
<td></td>
<td>Perc</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>None</td>
<td>Niessen et al.(32)</td>
</tr>
<tr>
<td></td>
<td>Perc</td>
<td>13</td>
<td>2 (15%)</td>
<td>AF (II)</td>
<td>Pneumothorax (II)</td>
<td>-</td>
<td>Cardioversion Chest drain</td>
<td>Thomson et al.(23)</td>
</tr>
<tr>
<td></td>
<td>Perc</td>
<td>9</td>
<td>3 (33%)</td>
<td>-</td>
<td>3 Bile duct occlusion (ns)</td>
<td>-</td>
<td>1 Bile duct stent, 2 ns</td>
<td>Silk et al.(26)</td>
</tr>
<tr>
<td></td>
<td>Perc</td>
<td>6</td>
<td>1 (17%)</td>
<td>SVT (I)</td>
<td>PV thrombosis (I)</td>
<td>-</td>
<td>None</td>
<td>Kingham et al.(25)</td>
</tr>
<tr>
<td></td>
<td>Open</td>
<td>22</td>
<td>3 (14%)</td>
<td>Bile duct occlusion (ns)</td>
<td>Portal vein occlusion (ns)</td>
<td>-</td>
<td>None</td>
<td>&quot;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ns</td>
<td>Cannon et al.(28)</td>
</tr>
<tr>
<td></td>
<td>ns</td>
<td>44</td>
<td>5 (11%)</td>
<td>-</td>
<td>Biliary stent occlusion (ns) Cholangitis (ns)</td>
<td>-</td>
<td>None</td>
<td>&quot;</td>
</tr>
</tbody>
</table>

Pancreas

<table>
<thead>
<tr>
<th>Target organ</th>
<th>Approach</th>
<th>No. Patients</th>
<th>No. complications (%)</th>
<th>Complication related to Electric pulses (grade)</th>
<th>Treatment site (grade)</th>
<th>Other (grade)</th>
<th>Intervention</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreas</td>
<td>Perc</td>
<td>14</td>
<td>4 (29%)</td>
<td>-</td>
<td>Pancreatitis (II)</td>
<td>Pneumothorax (II) Hematoma (I)</td>
<td>None Chest drain</td>
<td>Narayanann et al.(34)</td>
</tr>
</tbody>
</table>

"IRE FOR NON-THERMAL ABLATION: A SYSTEMATIC REVIEW"
## Chapter 6: Nausea (II)

### Antiemetics

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Nausea (II)</th>
<th>Antiemetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perc</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Open</td>
<td>27</td>
<td>4 (15%)</td>
</tr>
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<td></td>
<td></td>
<td></td>
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</tbody>
</table>

**Bagla et al. (35)**

<table>
<thead>
<tr>
<th>Kidney</th>
<th>Open</th>
<th>6</th>
<th>1 (17%)</th>
<th>SVT (I)</th>
<th>-</th>
<th>-</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Open</td>
<td>8</td>
<td>4 (50%)</td>
<td>-</td>
<td>Ureter obstruction (II)</td>
<td>Ureteral stenting</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adrenal ablation (ns)</td>
<td>ns ‡</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 Hematuria (I)</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

**Martin et al. (21)**

| Lung | Open | 4 | 2 (50%) | - | 2 Pneumothorax (I) | None |
|      | Perc | 2 | 1 (50%) | - | Parenchymal hemorrhage (I) | None |

**Thomson et al. (23)**

<table>
<thead>
<tr>
<th>Presacral</th>
<th>Perc</th>
<th>1</th>
<th>1 (100%)</th>
<th>-</th>
<th>Mild paresis (I)</th>
<th>None</th>
</tr>
</thead>
</table>

**Niessen et al. (33)**

<table>
<thead>
<tr>
<th>Lymph node</th>
<th>Perc</th>
<th>2</th>
<th>-</th>
<th>-</th>
<th>-</th>
<th>-</th>
</tr>
</thead>
</table>

**Thomson et al. (23)**

<table>
<thead>
<tr>
<th>Not specified</th>
<th>Perc</th>
<th>5</th>
<th>-</th>
<th>-</th>
<th>-</th>
<th>-</th>
</tr>
</thead>
</table>

**Thomson et al. (23)**

<table>
<thead>
<tr>
<th>Total, per organ</th>
<th>Perc</th>
<th>Open</th>
<th>129</th>
<th>21 (16%)</th>
<th>-</th>
<th>-</th>
<th>None</th>
</tr>
</thead>
</table>

**Thomson et al. (23)**

| Total, overall | Perc | Open | 194 | 43 (22%) | 8 (4%) | 26 (13%) | 8 (4%) |
Table 3 Efficacy of hepatic IRE

Note. – Perc = percutaneous; HCC = hepatocellular carcinoma; CRLM = colorectal liver metastasis; † Follow-up results reported for 54/65 tumors. * One patient was successfully retreated.

<table>
<thead>
<tr>
<th>Author</th>
<th>No. patients</th>
<th>No. lesions</th>
<th>Size (cm, median, range)</th>
<th>Approach</th>
<th>Tumor type, per patient</th>
<th>Primary technique effectiveness (%)</th>
<th>Secondary technique effectiveness</th>
<th>Follow-up (months)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannon et al.(28)</td>
<td>44</td>
<td>48</td>
<td>2.5 (1.1-5.0)</td>
<td>Open (14) Perc (28) Lap (2)</td>
<td>HCC (14) CRLM (20) Other (10)</td>
<td>97</td>
<td>-</td>
<td>6</td>
<td>95</td>
</tr>
<tr>
<td>Cheung et al.(24)</td>
<td>11</td>
<td>18</td>
<td>1.9 (1-6.1)</td>
<td>Perc</td>
<td>HCC (11)</td>
<td>67</td>
<td>18</td>
<td>72*</td>
<td></td>
</tr>
<tr>
<td>Kasivisvanathan et al.(29)</td>
<td>1</td>
<td>1</td>
<td>2.8</td>
<td>Perc</td>
<td>CRLM</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Kingham et al.(25)</td>
<td>28</td>
<td>54‡</td>
<td>1.0 (0.5-5.0)</td>
<td>Open (22) Perc (6)</td>
<td>HCC (2) CRLM (21) Other (5)</td>
<td>96</td>
<td>6</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>Silk et al.(26)</td>
<td>9</td>
<td>19</td>
<td>3.0 (1.0-4.7)</td>
<td>Perc</td>
<td>CRLM (8) Other (1)</td>
<td>ns</td>
<td>9</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Thomson et al.(23)</td>
<td>13</td>
<td>45</td>
<td>2.8 (1.0-8.8)</td>
<td>Perc</td>
<td>CRLM (6) Other (7)</td>
<td>67</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>106</td>
<td>185</td>
<td></td>
<td>Open (36) Perc (68) Lap (2)</td>
<td>HCC (27) CRLM (56) Other (23)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>
Table 4 Efficacy of pancreatic IRE

Note. – Perc = percutaneous; lap = laparoscopic; LAPC = locally advanced pancreatic carcinoma.* See table 1; ‡ 4/14 patients were excluded for efficacy analysis due to follow-up <3 months.

<table>
<thead>
<tr>
<th>Author</th>
<th>No. patients</th>
<th>Size (cm, median, range)</th>
<th>Approach</th>
<th>Follow-up (median, months)</th>
<th>Treatment effect</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martin et al.(22)*</td>
<td>54</td>
<td>3.2 (1-5.5)</td>
<td>Open (52) Lap (2)</td>
<td>15</td>
<td>Stable disease 15 Local progression 11 Distant progression 20.2 months (median)</td>
<td></td>
</tr>
<tr>
<td>Bagla et al.(35)</td>
<td>1</td>
<td>4.1</td>
<td>Perc</td>
<td>6</td>
<td>Stable disease 4 Local progression 2 Distant progression 1</td>
<td>6-month survival: 70%</td>
</tr>
<tr>
<td>Narayanan et al.(34)‡</td>
<td>7 LAPC</td>
<td>3.3 (2.5-7.0)</td>
<td>Perc</td>
<td>8.5 (4.0-14.0)</td>
<td>Stable disease 4 Local progression 2 Distant progression 1</td>
<td>6-month survival: 70%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3, 4 and 9 months</td>
</tr>
</tbody>
</table>
Discussion

Intentional cell death induced by IRE for tumor ablation has only been studied in the past few years. The potential advantage of preservation of extracellular matrix structures, in the absence of thermal coagulation had undergone extensive preclinical testing before it was introduced in the clinical setting. The results found in this review are further discussed below.

Safety

The electric fields applied in IRE can cause cardiac arrhythmias. Synchronized pulsing with the heart rhythm reduces this risk(16). This is confirmed by our results: with cardiac gating, only minor arrhythmias occurred with a total incidence of 2% (4/194). Based on this, we expect that with adequate synchronization the risk for severe arrhythmias in a patient without pre-existing cardiac abnormalities, is minimal. Moreover, uncontrolled muscle contractions were prevented with adequate muscle relaxants.

Hepatic IRE was associated with an overall complication rate of 16% (21/129). Numerous liver capsule punctures did not cause subcapsular hemorrhage, and pain appeared similar to pain after RFA(30). As a comparison, in a review on hepatic RFA in 3670 patients, overall complication rate was 9%, with rates of 7, 10, 10 and 32% for respectively percutaneous, laparoscopic, simple open and combined open RFA(37). IRE was mostly performed on tumors near or around portal pedicles and impaired patency of these structures caused by IRE occurred in 6/129 cases (5%)(25,26,28). Although IRE is believed to be primarily non-thermal, heat development immediately adjacent to the electrodes has been described(38), which may have caused thermal coagulation and subsequent occlusion of the bile duct that was in direct contact with one of the needles(26). As a safety precaution, placement of electrodes <2mm to central bile ducts, pancreatic ducts or intestines should thus be avoided. Overall, vascular and biliary structures were mostly preserved, which suggests that IRE may be a safer option than thermal ablation in this area. Further studies with longer follow-up are still needed to confirm these results.

The aim of pancreatic ablation is cytoreduction, leading to better symptom palliation, improved quality-of-life and prolonged survival(39,40). To this end, pancreatic RFA was previously investigated. However, due to the organ’s delicate nature and vulnerability to thermal injury, RFA proved unsuitable, with a high complication rate (28-40%) and mortality rate (7.5%)(39,41). With proven efficacy, a complication rate around 19% for IRE might be acceptable, although reported rates vary widely between studies. In favor of invasive treatment, Martin et al demonstrated comparable morbidity for patients with and without IRE after 4 months, with longer survival and better palliation in the IRE-group(22).
Efficacy
For patients with unresectable hepatic tumors also unsuitable for thermal ablation due to difficult location, chemotherapy with palliative intent is generally the treatment of choice(42). A new curative treatment option for these patients is therefore of great importance. IRE was used as ‘last resort’ in most patients. Thus, a primary technique effectiveness of 67-100% (and even higher for smaller tumors), is by all means promising, especially since these unresectable tumors can have a less favorable biological behavior than resectable tumors(43). Of note, tumors near large vessels did not appear to recur more frequently, which could suggest that treatment effect is indeed not impeded by heat-sink(25). Considering the limited quality of the data, larger prospective studies are needed to confirm these observations.

Current treatment of locally advanced pancreatic carcinoma consists of chemotherapy (usually gemcitabine or folfirinox), with or without radiotherapy. This leads to a modest increase in survival, often at the expense of severe side-effects(44,45). Two studies suggested a treatment benefit for IRE in terms of pain reduction and survival(22,34). Due to low patient number and combination of IRE with surgery, it is difficult to determine whether this benefit is indeed substantial. Future prospective trials should therefore aim to establish the outcome of IRE as stand-alone therapy, including quality-of-life registration. Due to scarcity of data, no definitive conclusions can be drawn with respect to renal and pulmonary IRE.

Limitations
New cancer treatments are typically best defined from phase III randomized trials comparing the new therapy with the current standard. However, in the field of local tumor ablation this has proven difficult: since its introduction decades ago the number of randomized trials remains very limited. Currently, literature on the clinical application of IRE is scarce with no randomized controlled trials. The majority of our data was extracted from case series and case reports with level 4 evidence(19) and are subject to several limitations: (1) possible publication bias of included retrospective studies and case reports, (2) the presented studies are without controls, low in patient number, and heterogeneous in study design and patient selection, (3) the retrospective design and short follow-up period of some studies may have led to underreporting and missing of (late) complications, (4) several studies combined efficacy results for different tumor types and sizes within one organ, or percutaneous and (combined) surgical procedures, and (5) duration of follow-up and imaging modalities varied across studies. These limitations precluded a meaningful quantitative meta-analysis, other than providing percentages of pooled measures across studies. These pooled measures may incorrectly assume homogeneity between studies. We recognize these limitations and
therefore our findings should be regarded with caution. This review presents a snapshot in
time in evaluation of IRE and both its content and message are subject to changes based on
future science that may be generated in this field. Nevertheless, despite these limitations,
the results of IRE with respect to safety and early efficacy found in this review appear
couraging.

Future directions
Several factors that may affect treatment outcome have been identified. Overall, local
recurrences were encountered more often after electroporation of larger tumors(23–25,28).
A hypothetical solution would be to increase either the number of probes required to treat
larger lesions, or the number of probe-repositionings. For example, a four-probe array with
an inter-probe distance of 2cm creates a 3cm ablation zone. Considering a 1cm tumor-free
margin, this would imply a maximum lesion size of 1cm for this four-probe array.
Misplacement of the probes by a margin of millimeters can result in residual tumor, so
accurate intraprocedural imaging is essential. Presumably, precise placement of larger probe
arrays is more difficult, especially since probe placement traversing through vulnerable
structures should be avoided(46).
The feasibility of real-time monitoring of hepatic IRE has been demonstrated in animal
studies. On ultrasound (US), the ablation zone immediately appears as a hypo-echoic area
with well-demarcated margins(14,47); contrast-enhanced computed tomography (ceCT)
shows a well-defined hypodense area, best visible on the portal venous phase(48,49). The
ablation zone on both imaging modalities correlates well with the pathologically defined
zone of cell death. However, results of real-time monitoring have been insufficiently related
to oncologic outcome in humans. Follow-up studies should therefore focus on immediate
and late imaging characteristics, related to oncologic outcome. Specific per-procedural
imaging guidelines could reassure the interventional radiologist when complete tumor
ablation has occurred, thereby increasing treatment efficacy.
During electroporation, cell membrane permeabilization leads to an increase in tissue
conductivity and depends on strength, number and duration of the pulses(50,51). Animal
studies have shown that the changes in electrical conductivity of the ablated tissue –
amongst others – determine ablation success. These changes could provide real-time
feedback on treatment outcome(51–53). However, organ-specific and tumor-specific electric
field dose-response studies are lacking, and much remains unknown about the clinical
possibilities to destroy malignant tissues with irregular geometries and heterogeneous
properties. Knowledge of the electrical and thermal properties of different tissue types
would allow for the identification of an optimal electric field, strong enough for maximized
tissue ablation, but weak enough to avoid excessive thermal effects(54).
As interventional oncologic therapies evolve, they are combined with other treatments such as transarterial chemo-embolization (TACE) and transarterial radio-embolization (TARE) to increase treatment effect. Similarly, a margin of reversibly electroporated tissue exists between the ablation zone and normal tissue directly after IRE. During this temporary permeability of the cell membranes, drugs like chemotherapeutics can travel freely into the cells within this zone, a process known as electrochemotherapy. Capitalizing on this largely unexplored principle, there may be a therapeutic advantage if IRE were combined with systemic chemotherapy to eradicate marginal remnant viable tumour cells\(^{55}\).

Results of several prospective trials are expectantly awaited. An overview of the registered ongoing and future clinical trials investigating the safety and efficacy of IRE for hepatic, pancreatic, renal and prostate tumors is available in the electronic supplement (appendix B).

**Conclusion**

This systematic review gives an extensive overview of the available evidence of the use of IRE for control of tumors near vulnerable structures such as blood vessels and bile ducts. With only case reports and case series the level of evidence of the available studies is low. Despite these limitations, the results suggest safe use of IRE, which is in accordance with results of pre-clinical studies. Early efficacy on smaller hepatic tumors near vascular structures and portal triads is promising, with reported ablation success reaching 90%, but rapidly decreasing with increasing tumor size. For unresectable pancreatic carcinoma, improved survival and significant pain reduction for IRE combined with radiochemotherapy is suggested, as compared to radiochemotherapy alone.

At this time, it appears that IRE is most suitable for tumors <3cm in diameter that are not eligible for resection or thermal ablation. While much research remains to be done, our results illustrate that the future of IRE appears promising. Alongside the other available local ablation techniques, IRE may become an important tool in the multimodality treatment of cancer in the near future.
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Reference list


(20) August PD. Common Terminology Criteria for Adverse Events v3.0 (CTCAE). 2006; 0:0–71.


